To the editor:

Recipient γδ T cells in graft-versus-host disease

We read with interest the paper by Maeda et al,[1] which concluded that host γδ T cells exacerbated graft-versus-host disease (GVHD) by promoting maturation of host antigen-presenting cells (APCs). In the "Introduction," the authors state that the role of host γδ T cells (in GVHD) is not known. However, we published a study in *Blood* examining the role of host lymphocytes in GVHD, including that of γδ T cells, 9 months prior to the article by Maeda et al.[2] Our work was not referenced by Maeda et al nor by Geoff Hill in his commentary.[3] Nonetheless, we do realize that our article appeared in print only 52 days before the article by Maeda and colleagues was submitted and thus, at least at the time of submission, they may have been unaware of our work. Because our published data differ considerably from the plenary paper, we think it is important to clarify the differences for readers of *Blood*. In contrast to the results of Maeda et al, we found no role for host γδ T cells in that the incidence and severity of skin disease (Figure 1A-B, reproduced from Anderson et al[2]), degree of weight loss (Figure 1C), and pathologic GVHD (Figure 1D) in wild-type and γδ T-cell–deficient recipients were indistinguishable. Also, unlike Maeda et al, we found that recipients deficient in αβ T cells had more severe and rapid GVHD relative to T-replete hosts, and on the basis of further experimentss we attributed this result to missing host $CD4^+CD25^+$ T regulatory cells.[2]

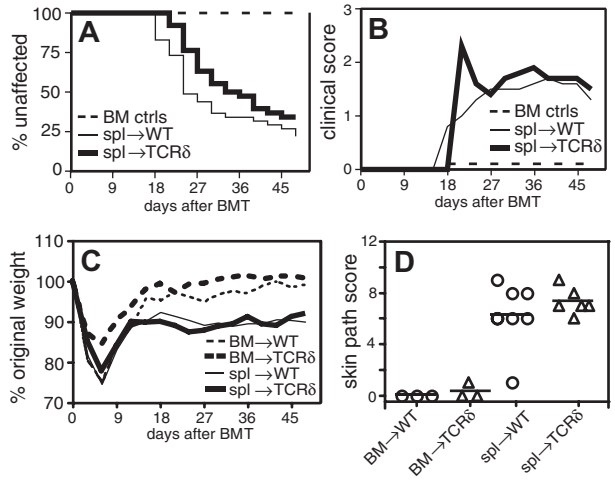

Figure 1. γδ T-cell–deficient recipients do not have increased incidence or severity of GVHD. Combined data from 3 experiments. On day 0, BALB/c (H-2^d) recipient mice were lethally irradiated and reconstituted with 8×10^6 T-cell–depleted B10.D2 (H-2^d) bone marrow (BM) cells alone (n = 28, both recipient types) or BM plus 10^7 B10.D2 spleen cells (spl): wild-type (WT) recipients (n = 41) or TCR$\delta^{-/-}$ recipients (n = 38). (A) Incidence of clinical skin GVHD. (B) Clinical skin score. Average clinical score for mice affected with GVHD (unaffected mice are excluded). BM control mice did not get GVHD and are represented on the graph as scoring 0. (C) Weight loss. (D) Pathologic skin disease. Representative mice were killed for pathologic analysis, and histologic cutaneous GVHD was scored by a dermatopathologist blinded to experimental groups.

The model systems used in the 2 papers were quite different, possibly explaining the divergent results. We used a major histocompatibility complex (MHC)–matched model (B10.D2→BALB/c; H-2^d) akin to the majority of human allogeneic stem cell transplantations, whereas Maeda et al used 3 MHC-mismatched models. These MHC-mismatched models resulted in hyperacute GVHD with substantial early lethality, likely due at least in part to massive cytokine release.[4,5] In contrast, the B10.D2→BALB/c model yields a more chronic form of GVHD that is nonlethal and characterized by a T-cell–infiltrative pathology involving the skin with less penetrance in the liver and bowel. Furthermore, the γδ T-cell–deficient mice we used were backcrossed to BALB/c, whereas those used by Maeda et al were on the C57Bl/6 background, and it is possible that the 2 strains may have different responses in the absence of γδ T cells. We wonder whether Maeda et al have examined GVHD in C57Bl/6 γδ T-cell–deficient recipients with MHC-matched, minor histocompatibility antigen–mismatched donors. Also, since Maeda et al suggest that γδ T cells promote host APC maturation, a potential mechanistic explanation for the different experimental findings could be that the B10.D2→BALB/c model is less reliant on host APCs than are MHC-disparate models.[5-7] Nonetheless, our data clearly indicate that the roles of γδ T cells differ by situation, and particularly, since we studied an MHC-matched situation that resembles the vast majority of human transplantations, and considering that γδ T cells may provide antipathogen immunity,[8,9] the conclusion that γδ T cells should be targeted as a means of GVHD reduction should be made with caution.

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Response:

The role of γδ T cells in graft-versus-host disease

Anderson et al are right to remind us of the important limitations of mouse models in the dissection of complex graft-versus-host disease (GVHD) biology, particularly when results from different models conflict. Although our conclusions that host γδ T cells regulated intestinal acute GVHD[1] are also supported by another group,[2] we agree with Anderson and colleagues' elegant summary of potential causes for discrepancies between the models. We were unaware of their work prior to the submission of our manuscript, and we did not examine the role of host γδT cells in minor histocompatibility antigen–mismatched strain combinations. Since GVHD of the skin dominates their model,[3] their data might be reconciled with ours if host γδ T cells contribute to the inflammation of intestinal acute GVHD but not to fibrotic skin changes characteristic of chronic GVHD. In any event, we wholeheartedly concur that all insights from animal models must be extrapolated to human patients with caution, and that the efficacy of any approach must be verified in well-designed, carefully controlled clinical trials.[4]

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To the editor:

Assessing the risk of inhibitor formation with different factor VIII products

The article by Goudemand et al[1] dealing with the influence of different types of factor VIII (FVIII) concentrates on the incidence of factor VIII inhibitors in previously untreated patients with severe hemophilia A is interesting and timely. The authors retrospectively analyzed 2 previously reported cohorts that had been treated with plasma-derived (pd) FVIII[2] or recombinant (r) FVIII,[3] updating the cohorts with a few additional patients not included in the previous publications. The perusal of this article leaves me with some questions that warrant comments from the authors.

The main question deals with the validity of comparing inhibitor incidence in very different cohorts. Although the authors state that the interval of inhibitor testing was similar for the 2 cohorts, 13 (23%) of 56 patients from the cohort treated with pdFVIII were actually tested only once per year, whereas patients from the rFVIII cohort were tested every 3 months (84%) or every 6 months (16%). This difference in frequency of inhibitor testing is critical, because more frequent testing is more likely to detect transient or low-titer inhibitors that may be of little clinical relevance but impinge upon inhibitor incidence. Indeed, previously untreated patients included in studies carried out to license FVIII products (and thus frequently assessed for inhibitors) demonstrate a more than 3-fold higher incidence of inhibitors than patients treated in the frame of postlicensure studies.[4] Nevertheless, the Kaplan-Meier analysis carried out by Goudemand et al[1] considers patients tested only annually as not having developed an inhibitor up to the first year. Another questionable point is that in 10 patients of the pdFVIII cohort treated before 1991, the quantitative Bethesda inhibitor assay was used only to confirm inhibitors suspected on the basis of a semiquantitative test based upon the partial thromboplastin time, whereas all the rFVIII-treated patients were evaluated from the onset using the Bethesda assay.[1] Considering these differences, the adjusted relative risk of inhibitor formation calculated by the authors may be substantially biased in favor of pdFVIII treatment.

Despite these limitations, the study of Goudemand et al[1] and other smaller retrospective studies[5-7] hint that there may be a difference between different types and source of FVIII in determining the occurrence of inhibitors in previously untreated patients with hemophilia A. However, only prospective controlled studies can truly address this issue. Such studies are certainly warranted, and regulatory authorities such as the Food and Drug Administration (FDA) in the United States and the European Agency for the Evaluation of Medicinal Products (EMEA) should prompt FVIII manufacturers to tackle this issue.

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